Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Section 7, pages 25-39

7. Integrated review of effectiveness

7.1. Mechanism of action

Clinical pharmacology studies are listed in Table 5, "Clinical pharmacology trials.," on page 9. The sponsor has cited studies indicating that 60% rigidity on penile plethysmography is adequate for penetration. This has been the basis for evaluation of effects of sildenafil in the clinic.

7.1.1. Single-dose studies

7.1.1.1. Mixed etiology

Study 148-105[1] was a randomized, double-blind, 4-period (placebo, 25 mg, 50 mg, and 100 mg) single-dose crossover study in 54 subjects organic or psychogenic erectile dysfunction (but not spinal cord injury). During each period, subjects underwent penile plethysmography during a 20-minute videotape of sexual activity (beginning 30 minutes after dosing) and for a 1-hour period following it. The mean duration of 60% rigidity was 0.06 minutes on placebo, 0.53 minutes on 25 mg, 0.39 minutes on 50 mg, and 0.95 minutes on 100 mg[2].

7.1.1.2. Psychogenic etiology

Study 148-351[3] was a randomized, double-blind, 4-period (placebo, 10 mg, 25 mg, and 50 mg) single-dose crossover study in 12 subjects with psychogenic erectile dysfunction. During each period, subjects underwent penile plethysmography during presentation of visual sexual stimulation (beginning 30 minutes after dosing) and for a 2.5-hour period following it. The mean duration of 60% rigidity at the tip of the penis was 2.9 minutes on placebo, 19 minutes on 10 mg, 26 minutes on 25 mg, and 27 minutes on 50 mg.

Study 148-360[4] was a randomized, double-blind, 2-period (placebo and 50 mg) single-dose crossover study in 17 subjects with psychogenic erectile dysfunction. Subjects underwent a 1-hour penile plethysmography, accompanied by visual sexual stimulation, beginning 10 minutes after dosing. Although the mean duration of erection was several-fold greater after sildenafil, the difference was not statistically significant.

Study 148-369[5] was a randomized, double-blind, 2-period (placebo and 100 mg) single-dose crossover study in 16 subjects with psychogenic erectile dysfunction. Two separate crossovers studies were conducted in the same subjects. Subjects underwent penile plethysmography, accompanied by visual sexual stimulation, 4 hours after dosing and then 2 hours after dosing. Erections of 60% rigidity lasted 3-times as long with sildenafil at 2 hours, and 2-times as long as placebo at 4 hours. Duration of erections correlated poorly with plasma levels of sildenafil or UK-103,320.

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1. *Study 148-105: A double-blind, randomised, placebo controlled, four-way crossover study to investigate the efficacy, safety and toleration of single oral dose of sildenafil (25, 50, and 100 mg) in patients with male erectile dysfunction.* on page 124.
2. Analyses focussed on means may have been sub-optimal in this and the other clinical pharmacology studies described here. Many subjects, particularly on placebo, had no erections, and, as a consequence, the means do not represent a typical response.
3. *Study 148-351: A double blind, randomised, placebo controlled, four way crossover study followed by a double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of UK-92,480 (sildenafil) in patients with erectile dysfunction with no established organic cause.* on page 184.
4. *Study 148-360: A double-blind, randomised, placebo controlled, two-way crossover study to investigate the onset of action of single oral doses of UK-92,480 (sildenafil) 50mg in patients with penile erectile dysfunction without an established organic cause.* on page 201.
5. *Study 148-369: A double blind, randomised, placebo controlled, sequential design, two way crossover study to investigate the duration of action of a single oral dose of sildenafil (100 mg) on penile erectile activity during visual sexual stimulation in patients with male erectile dysfunction without an established organic cause.* on page 222.

7.1.1.3. Diabetes

Study 148-357[6] was a randomized, double-blind, 3-period (placebo, 25 mg, and 50 mg) single-dose crossover study in 21 subjects with erectile dysfunction and diabetes. Subjects underwent penile plethysmography from 15 minutes prior to dosing, through presentation of visual sexually stimulating materials, for a total of 2 hours after dosing. The mean duration of 60% rigidity at the tip of the penis was 1.3 minutes on placebo, 2.7 minutes on 25 mg, and 4.3 minutes on 50 mg.

7.1.1.4. Spinal cord injury

Study 148-358[7] was a randomized, double-blind, 2-period (placebo and 50 mg) single-dose crossover study in 27 subjects with erectile dysfunction and spinal cord injury. Subjects underwent penile plethysmography in association with 4-minute periods of vibratory stimulation 0.5, 1, and 1.5 hours after study drug administration. Although there were statistically significant sildenafil-placebo differences claimed for median durations of erections, estimates of mean effects, by time after dosing, were analyzed neither by the sponsor nor by the reviewers.

7.1.2. Multiple-dose studies

7.1.2.1. Psychogenic etiology

Study 148-350[8] was a randomized, double-blind, 2-period (placebo and sildenafil 25 mg tid for 7 days) multipile-dose, crossover study in 16 subjects with psychogenic erectile dysfunction. On day 7, subjects underwent penile plethysmography during and for 10 hours following presentation of visual sexual stimulation. The mean duration of 60% rigidity at the tip of the penis was 7.4 minutes on placebo and 36 minutes on sildenafil.

7.1.3. Effects by etiology of erectile dysfunction

The sponsor studied populations with erectile dysfunction presumably resulting from psychogenic (no known organic) causes, diabetes mellitus, spinal cord injury, and mixed organic and psychogenic etiology[9], similar to populations in principal effectiveness studies discussed in section 7.2 on page 27. The results are consistent with a beneficial effect of sildenafil on the ability of subjects with erectile dysfunction to attain an erection suitable for intercourse, regardless of the etiology of the disease. However, the data showing an effect in subjects with diabetes and spinal cord injury are much less compelling than are the data in erectile dysfunction of psychogenic and mixed etiologies.

7.1.4. Time course of effects after a dose

The time course of effects on erectile function has not been well studied. A single study in subjects with psychogenic erectile dysfunction showed greater sildenafil-placebo differences at 2 hours than at 4 hours. Most studies evaluated erectile function in the first hour after study drug administration.

7.1.5. Time course of effects with repetitive dosing

There was only one study, in subjects with psychogenic erectile dysfunction, with penile plethysmography after multiple daily dosing. This study did not have an evaluation of erectile function after the first dose, so it is difficult to interpret with respect to the development of effects with successive dosing. In this population, sildenafil was associated with erections of longer duration than was placebo, and the range of durations was not materially different than that seen in single-dose studies with subjects having psychogenic erectile dysfunction.

7.1.6. Relationship between dose and erectile function

Single-dose studies in erectile dysfunction of either psychogenic or mixed etiologies explored the dose range from 25 to 100 mg. The results suggest that 25 mg is substantially better than placebo and that 100 mg is not likely to be on the plateau of the dose-response curve.

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6. *Study 148-357: A multi-centre, double blind, randomised, placebo controlled, three way crossover study to investigate the efficacy of single oral doses of sildenafil (UK-92,480) in diabetic patients with penile erectile dysfunction.* on page 195.
7. *Study 148-358: A two stage, double blind, placebo-controlled study to assess the efficacy and safety of oral doses of sildenafil (UK-92,480) in spinal cord injury patients with erectile dysfunction.* on page 197.
8. *Study 148-350: A double blind, randomised, placebo controlled, two way crossover pilot study to investigate the efficacy and safety of UK-92,480 (sildenafil, 25mg tid for 7 days) in patients with impotence.* on page 183.
9. The term 'mixed etiology' should be interpreted with respect to the population. Individual subjects could have organic, psychogenic, or combined causes for their erectile dysfunctions.

7.1.7. Relationship between plasma levels and erectile function

Most studies were inadequately designed (admittedly difficult) or were under-powered to assess the relationship between plasma levels of sildenafil or metabolite UK-103,320 and erectile function. The data are suggestive that plasma levels are not highly predictive of response.

7.2. Effects on sexual performance

7.2.1. Methods of assessment

7.2.1.1. Primary

The sponsor developed a standard questionnaire for obtaining information pertaining sexual function. Although some early studies were performed with end points pertaining to the ability to attain erections or some measure of subject satisfaction, the standard questionnaire, and in particular 2 questions, pertaining to sexual performance, were the primary end points of most studies of effectiveness.

> *[3] Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?*
>
> *[4] Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?*

Responses to these questions (and the other 13 on the IIEF) were categorical and the sponsor's analyses assigned the categories naturally ordered integral values. Responses to IIEF questions 3 and 4 were scored as 0 for no attempts, 1 for never or rarely successful, etc., up to 5 for always or almost always successful. All randomized subjects with a post-randomization assessment were included in the sponsor's ITT analyses. The sponsor's analyses were LOCF, which tends to make placebo, which had a higher withdrawal rate, better than it otherwise would be.In analyzing studies that used these questions as the primary end point, the sponsor prospectively stated that a study would be considered 'positive' only if the p-value associated with both questions was <0.05.

For fixed-dose studies, the null hypothesis was that the slope of the dose-response curve was zero. All analyses were intent-to-treat, with last observation carried forward. Since withdrawal rates were always higher on placebo, carrying forward the last observation is more conservative than assigning a worst rank to withdrawals.

Validation of the sponsor's sexual function questionnaire is reviewed in Appendix A3 *Development and validation of the primary efficacy instrument (International Index of Erectile Function; IIEF).* on page 87. The validation procedure appears to have established this instrument as being specific for sexual function, but the relationship between responses to the questionnaire and actual performance is nowhere addressed.

7.2.1.2. Supportive

The other IIEF questions, generally treated by the sponsor as supportive, addressed other aspects of sexual function or sense of well-being, and these were analyzed in a manner similar to the primary questions.

Many studies incorporated a global assessment question, pertaing to satisfaction with treatment, a general quaility of life questionnaire, and a partner questionnaire, to which a minority of partners responded.

All studies included an event log wherein subjects reported taking doses of study drug, attempted intercourse, and successful intercourse.

7.2.2. Dose dependence

7.2.2.1. Common characteristics of fixed-dose studies

There were 6 randomized, double-blind, parallel, placebo-controlled, fixed-dose studies, evaluating doses in the range from 5 to 200 mg in the home setting. Some characteristics of these studies are shown in Table 4 on page 8. Four of these studies used the IIEF—Study 148-102, 148-106, 148-361, and 148-364—although questions 3 and 4 were the primary end points in only 3 of them.

These studies recruited men age >18, with erectile dysfunction[10] of >6 months' duration, and in a heterosexual relationship for >6 months. Subjects were excluded for (1) anatomical deformities such as severe penile fibrosis, (2) other sexual disorders such as hypoactive sexual desire, (3) elevated prolactin (3x ULN) or low free testosterone (20% below LLN), (4) major, uncontrolled psychiatric disorders, (5) history of alcohol or drug abuse, (6) history of major hematologic, renal, or hepatic disorder, (7) erectile dysfunction following spinal cord injury, (8) uncontrolled diabetes or diabetic retinopathy, (9) stroke or myocardial infarction within 6 months, (10) cardiac failure, unstable angina, ECG ischemia, or life-threatening arrhythmia within 6 months, (11) blood pressure outside 90/50 to 170/100 mmHg, (12) active peptic ulcer disease or bleeding disorder, (13) any clinically significant baseline laboratory abnormality, (14) need for anticoagulants, nitrates, androgens, or trazodone, (15) need for aspirin or NSAIDs and a history of peptic ulcer disease, (16) unwillingness to cease use of vacuum devices, intracavernosal injection, or other therapy for erectile dysfunction, (17) other experimental drug use within 3 months, or (18) history of retinitis pigmentosa.

Studies had a 4-week treatment-free run-in period during which baseline sexual performance data were collected, after which subjects were randomized and followed for 12 or 24 weeks.

7.2.2.2. Fixed-dose studies assessed by IIEF

Four fixed-dose studies assessed using the IIEF are described in Table 15 below. All of these studies excluded subjects with erectile dysfunction attributable to spinal cord injury.

Table 15. Fixed-dose studies utilizing the IIEF.

Study	Doses (mg)				N	Weeks	Etiology (%)			Diabetes (%)
	25	50	100	200			Organic	Psychogenic	Mixed	
148-102	✓	✓	✓		532	24[a]	78	9	13	15
148-106		✓	✓	✓	497	12	58	17	25	17
148-361[b]	✓	✓	✓	✓	254	12	49	7	44	?
148-364	✓	✓	✓		514	12	43	32	25	9

a. Primary end point was at week 12, but the double-blind period was 24 weeks.
b. Primary end point was IIEF question 1: ability to attain erection.

7.2.2.2.1. Analyses of sexual performance by IIEF

The sponsor's analyses of the sexual performance questions in these 4 studies are shown in Table 16 below.

10. 'the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance'

Table 16. ITT analyses of IIEF questions 3 and 4 (fixed-dose studies).

	Study	Baseline Q[a]	Placebo		Sildenafil								P^b
					25 mg		50 mg		100 mg		200 mg		
			n	Q	n	Q	n	Q	n	Q	n	Q	
How often were you able to penetrate your partner?	148-102	2.0	190	2.3	95	3.3	100	3.7	96	4.0	—	—	<0.0001
	148-106	1.8	109	2.2	—	—	116	3.5	112	3.7	112	3.5	<0.0001
	148-361	1.9	58	1.9	61	3.4	64	3.7	66	3.7	—	—	<0.0001
	148-364	2.2	117	2.2	121	3.2	123	3.7	120	3.8	—	—	<0.0001
How often were you able to maintain your erection after penetration?	148-102	1.6	189	2.2	95	3.2	100	3.5	96	3.9	—	—	<0.0001
	148-106	1.5	109	1.7	—	—	115	3.2	112	3.6	112	3.4	<0.0001
	148-361	1.7	58	1.9	61	3.3	64	3.7	65	3.7	—	—	<0.0001
	148-364	1.8	115	2.0	119	3.0	122	3.4	118	3.6	—	—	<0.0001

a. Mean value for question.
b. P-value for non-zero slope to dose-response.

None of the sponsor's analyses were recapitulated by the reviewers. However, for 2 studies for which the complete SAS datasets were provided by the sponsor, the reviewers performed sub-group analyses based upon baseline characteristics likely to have some effect on disease severity. These results are summarized in Table 17 below. These results are entirely consistent with the sponsor's highly statistically significant treatment effect, strongly support effectiveness in subjects with erectile dysfunction of organic, psychogenic, or mixed etiology, strongly support effectiveness with or without a history of nocturnal erections, strongly support effectiveness in erectile dysfunction of relatively short or long duration (less than or greater than 3 years), and strongly support effectiveness with or without a history of previous medical or mechanical treatment of erectile dysfunction. Less compelling is the evidence from these studies that sildenafil is effective in subjects with diabetes mellitus.

Table 17. Sub-group analyses of IIEF questions 3 and 4[a] (Studies 148-102 and 148-364).

	N		How often were you able to penetrate your partner?						How often were you able to maintain your erection after penetration?					
	148-		148-102			148-364			148-102			148-364		
	102	364	Intcpt	Slope	P^b	Intcpt	Slope	P	Intcpt	Slope	P	Intcpt	Slope	P
Etiology														
Organic	411	165	0.2±0.1	16±2	0.0001	0.1±0.2	13±3	0.0001	0.4±0.1	15±2	0.0001	0.4±0.2	12±3	0.003
Psychogenic	50	129	0.2±0.2	23±5	0.0001	0.3±0.2	15±3	0.0001	0.1±0.2	28±5	0.0001	0.6±0.2	15±3	0.0001
Mixed	70	219	0.7±0.3	19±6	0.003	0.5±0.2	11±3	0.001	1.1±0.3	16±5	0.005	0.6±0.2	12±3	0.003
Nocturnal erections														
Yes	308	335	0.5±0.1	18±2	0.0001	0.2±0.1	16±2	0.0001	0.7±0.1	18±2	0.0001	0.4±0.1	17±2	0.0001
No	175	151	0.0±0.1	16±3	0.0001	0.4±0.2	11±3	0.002	0.1±0.2	15±3	0.0001	0.7±0.2	8±3	0.02
Duration														
<3 years	325	177	0.1±0.1	19±2	0.0001	0.6±0.2	8±3	0.008	0.5±0.1	17±2	0.0001	0.7±0.2	11±3	0.0007
>3 years	206	336	0.5±0.1	13±3	0.0001	0.2±0.1	15±2	0.002	0.5±0.1	17±3	0.0001	0.5±0.1	13±2	0.002
Previous treatment														
Yes	284	375	0.4±0.1	16±3	0.0001	0.4±0.1	12±2	0.0001	0.6±0.1	15±3	0.0001	0.6±0.1	12±2	0.0001
No	247	138	0.1±0.1	17±2	0.0001	0.3±0.2	15±4	0.0001	0.3±0.1	18±3	0.0001	0.5±0.2	14±3	0.0001
Diabetes mellitus														
Yes	72	44	0.4±0.2	5±5	0.29	0.3±0.3	2±5	0.72	0.5±0.2	8±5	0.11	0.4±0.2	5±4	0.26
No	459	469	0.3±0.1	18±2	0.0001	0.4±0.1	14±2	0.0001	0.5±0.1	17±2	0.0001	0.6±0.1	13±2	0.0001

a. Reviewers' LOCF analyses; slope of dose-response (change in score per g)

b. P-value for non-zero slope to dose-response analysis of treatment alone.

7.2.2.2.2. Analyses of other IIEF questions

Other aspects of the IIEF were consistent with the effectiveness of sildenafil, as shown in Table 18 below. On all questions except the one pertaining to frequency of desire, the individual studies are consistent and highly statistically significant, so appropriate adjustments for multiple end points are not at issue. For the frequency of desire question, the 2 US studies (148-102 and 148-106) show at trend toward a treatment benefit and the 2 European studies show high statistical significance.

Table 18. ITT analyses of supportive IIEF questions at week 12 (fixed-dose studies)[a].

Question	Study	Baseline	Placebo		Sildenafil								P^b
					25 mg		50 mg		100 mg		200 mg		
			n	Q	n	Q	n	Q	n	Q	n	Q	
Able to get erection	148-102	2.5	189	2.9	95	3.8	100	4.0	97	4.4	—	—	<0.0001
	148-106	2.3	108	2.3	—	—	116	3.3	112	3.7	112	3.7	<0.0001
	148-361	2.1	58	2.1	—	—	61	3.8	64	3.8	66	3.9	<0.0001
	148-364	2.5	118	2.4	123	3.4	125	3.7	120	3.9	—	—	<0.0001
Erections hard enough	148-102	2.1	190	2.1	95	3.3	99	3.8	97	4.0	—	—	<0.0001
	148-106	1.8	110	2.0	—	—	116	3.3	112	3.6	112	3.4	<0.0001
	148-361	1.9	58	2.0	—	—	61	3.5	64	3.8	66	3.8	<0.0001
	148-364	2.2	118	2.2	123	3.3	125	3.6	117	3.9	—	—	<0.0001
Difficulty maintaining erection	148-102	1.5	190	2.1	95	3.2	100	3.6	97	3.9	—	—	<0.0001
	148-106	1.5	110	1.7	—	—	116	3.4	113	3.6	112	3.4	<0.0001
	148-361	1.6	58	1.7	—	—	61	3.2	64	3.5	66	3.6	<0.0001
	148-364	1.7	114	1.9	118	3.1	124	3.6	118	3.6	—	—	<0.0001
Confidence in erection	148-102	1.6	190	2.1	95	2.7	98	3.3	96	3.4	—	—	<0.0001
	148-106	1.6	108	1.8	—	—	113	3.0	111	3.2	110	3.1	<0.0001
	148-361	1.7	57	1.9	—	—	61	3.2	64	3.4	65	3.4	<0.0001
	148-364	2.0	117	2.3	120	3.0	123	3.2	117	3.5	—	—	<0.0001
Attempted intercourse	148-102	1.9	191	2.7	95	3.1	100	3.0	97	3.6	—	—	<0.0001
	148-106	2.0	110	2.7	—	—	116	3.3	113	3.3	112	3.2	0.001
	148-361	1.5	58	1.8	—	—	61	2.6	64	2.8	66	2.9	<0.0001
	148-364	2.0	114	2.4	120	3.0	123	3.1	117	3.3	—	—	<0.0001
Satisfaction of intercourse	148-102	1.8	191	2.3	94	3.4	100	3.7	97	3.9	—	—	<0.0001
	148-106	1.6	110	1.9	—	—	116	3.2	112	3.5	112	3.6	<0.0001
	148-361	1.8	58	1.9	—	—	61	3.4	64	3.7	66	3.6	<0.0001
	148-364	1.9	114	2.1	118	3.1	122	3.5	116	3.8	—	—	<0.0001
Enjoyment of intercourse	148-102	1.8	191	2.3	94	3.0	100	3.6	97	3.8	—	—	<0.0001
	148-106	1.8	110	1.9	—	—	115	3.1	112	3.2	112	3.2	<0.0001
	148-361	1.8	58	1.8	—	—	61	2.8	64	3.1	66	3.3	<0.0001
	148-364	2.0	113	2.2	118	2.9	123	3.4	117	3.4	—	—	<0.0001
Frequency of ejaculation	148-102	3.1	189	3.2	93	4.0	97	4.2	97	4.3	—	—	<0.0001
	148-106	2.7	108	2.9	—	—	116	3.6	110	3.7	111	3.6	0.0002
	148-361	2.8	55	2.8	—	—	61	3.8	63	4.2	65	4.0	<0.0001
	148-364	3.0	118	3.2	118	3.5	121	3.9	120	4.0	—	—	<0.0001

Table 18. ITT analyses of supportive IIEF questions at week 12 (fixed-dose studies)[a].*(Continued)*

Question	Study	Base-line	Placebo		Sildenafil								P^b
					25 mg		50 mg		100 mg		200 mg		
			n	Q	n	Q	n	Q	n	Q	n	Q	
Frequency of orgasm	148-102	3.0	190	3.2	94	3.5	100	4.2	97	4.1	—	—	<0.0001
	148-106	2.7	109	2.9	—	—	116	3.6	113	3.7	112	3.5	0.0002
	148-361	2.8	55	2.7	—	—	61	3.7	63	4.1	65	3.9	<0.0001
	148-364	2.8	118	2.8	117	3.4	121	3.6	119	3.8	—	—	<0.0001
Frequency of desire	148-102	3.5	190	3.3	95	3.3	100	3.5	97	3.6	—	—	0.2
	148-106	3.3	109	3.3	—	—	115	3.5	112	3.5	111	3.5	0.4
	148-361	3.0	55	3.0	—	—	61	3.3	63	3.6	65	3.7	0.0005
	148-364	3.3	116	3.2	120	3.2	123	3.5	119	3.6	—	—	0.001
Rating of desire	148-102	3.2	190	3.2	95	3.3	100	3.4	97	3.3	—	—	0.2
	148-106	3.1	110	3.1	—	—	116	3.3	112	3.3	111	3.4	0.008
	148-361	2.8	56	2.8	—	—	61	3.0	63	3.4	66	3.5	0.0004
	148-364	3.1	116	3.1	118	3.2	123	3.3	119	3.4	—	—	0.01
Satisfaction with sex life	148-102	1.9	190	2.4	95	3.1	100	3.4	97	3.6	—	—	<0.0001
	148-106	1.9	109	2.1	—	—	116	3.2	112	3.4	111	3.5	<0.0001
	148-361	1.9	56	2.0	—	—	61	3.2	63	3.4	66	3.5	<0.0001
	148-364	2.1	118	2.3	118	3.1	123	3.4	117	3.6	—	—	<0.0001
Satisfaction with relationship	148-102	2.7	187	3.1	94	3.7	100	3.8	95	4.1	—	—	<0.0001
	148-106	2.5	108	2.6	—	—	116	3.6	111	3.8	110	3.8	<0.0001
	148-361	2.5	56	2.7	—	—	61	3.7	63	3.9	66	4.0	<0.0001
	148-364	2.6	118	2.9	116	3.3	122	3.7	116	3.8	—	—	<0.0001

a. Sponsor's analyses.
b. P-value for non-zero slope to dose-response.

For the frequency of desire question, the 2 US studies (148-102 and 148-106) show at least a trend toward a treatment benefit and the 2 European studies show high statistical significance in favor of a benefit.

7.2.2.2.3. Analyses of event logs

The sponsor's analyses of event logs were based upon the proportion of all attempts that were successful. These results are included in some of the study reports.

The reviewers' analyses of event logs, derived from fixed-dose studies for which full SAS datasets were available, are summarized in Table 19 below. The results illustrate that subjects in these trials were not profoundly incapacitated. One-third to one-half of subjects had successful intercourse during a treatment-free run-in period. The number of attempts at intercourse was not much affected by the treatment, so the sponsor's analyses of success rates was valid and informative. Whether assessed by the number of successful attempts per subject per week, the proportion of attempts that were successful, or the proportion of subjects who were successful at least once during the study, sildenafil treatment groups had markedly better sexual performance success than did placebo. However, there appeared to be very little to distinguish among the doses (25 to 100 mg).

Table 19. Successful intercourse by event logs (fixed-dose studies).

		Study	Placebo	Sildenafil		
				25 mg	50 mg	100 mg
Attempts	Total	148-102	14004	7023	7795	7055
		148-364	3705	4313	4192	4062
	Per subject mean	148-102	65	69	73	66
		148-364	29	34	32	32
	Per subject per week	148-102	2.7	2.9	3.0	2.8
		148-364	2.4	2.8	2.7	2.7
Successes	Total	148-102	3388	2701	3994	3627
		148-364	481	1635	1808	1879
	Per subject mean	148-102	16	26	37	34
		148-364	3.8	13	14	15
	Per subject per week	148-102	0.7	1.1	1.5	1.4
		148-364	0.3	1.1	1.2	1.3
Success by attempts	(%)	148-102	24	38	51	51
		148-364	13	38	43	46
Success by subjects (%)	During run-in	148-102	43	33	47	48
		148-364	32	42	33	31
	Double-blind period	148-102	69	86	89	92
		148-364	53	79	91	82

7.2.3. Titration studies

7.2.3.1. Common characteristics of titration studies

There were 8 randomized, double-blind, parallel or crossover, placebo-controlled studies in which subjects' dose of randomized treatment could be modified, as considered appropriate by the investigator, to achieve maximum benefit or to avoid adverse effects. These studies evaluated doses in the range from 25 to 100 mg in the home setting. Some characteristics of these studies are shown in Table 4 on page 8. Five of these studies used the IIEF, although questions 3 and 4 were the primary end points in only 3 of them[11].

The inclusion and exclusion criteria in these studies were similar to those in fixed-dose studies, except that Study 148-104 was restricted to subjects with diabetes mellitus and Study 148-367 was restricted to subjects with spinal cord injury.

7.2.3.2. Titration studies assessed by IIEF

The 4 titration studies are described in Table 20 below.

Table 20. Titration studies utilizing the IIEF.

Study	Doses (mg)			N	Weeks	Etiology (%)			Diabetes (%)
	25	50	100			Organic	Psychogenic	Mixed	
148-103	✓	✓	✓	329	12	59	15	26	10
148-104		✓	✓	268	12	96	—	4	100
148-363	✓	✓	✓	315	26[a]	30	32	37	16
148-367[b]		✓	✓	178	6	100	0	0	<1

a. Primary analysis at week 12.
b. Crossover design, subjects with spinal cord injury, 6 weeks per arm.

[11] A fourth study was part if the IIEF validation program and is discussed elsewhere.

7.2.3.2.1. Analyses of sexual performance by IIEF

The sponsor's analyses of the sexual performance questions in these 4 studies are shown in Table 21 below.

Table 21. ITT analyses of IIEF questions 3 and 4 (titration studies).

	Study	Pop'n	Baseline	Placebo		Sildenafil		P[a]
				n	Q	n	Q	
How often were you able to penetrate your partner?	148-103	Mixed	2.0	138	2.3	138	3.9	<0.0001
	148-363	Mixed	1.9	101	2.2	124	3.5	<0.0001
	148-104	Diabetes	1.7	126	2.0	131	3.2	<0.0001
	148-367	Cord	2.0	158	2.2	155	3.8	<0.0001
How often were you able to maintain your erection after penetration?	148-103	Mixed	1.5	138	1.8	137	3.6	<0.0001
	148-363	Mixed	1.6	116	2.1	136	3.5	<0.0001
	148-104	Diabetes	1.4	125	1.6	131	2.9	<0.0001
	148-367	Cord	1.5	158	1.7	155	3.6	<0.0001

a. P-value from two-sample t-test.

None of the sponsor's analyses were recapitulated by the reviewers. However, for the two of these studies for which unabridged SAS datasets were provided, the reviewers performed sub-group analyses, based upon baseline characteristics likely to have some relationship to disease severity. These results are summarized in Table 22 below. For most sub-groups, the sildenafil-placebo differences were highly statistically significant for both effectiveness questions. This was true for diabetic subjects in Study 148-363; in Study 148-103, the difference was less statistically compelling, although entirely consistent with Study 148-363.

Table 22. Sub-group analyses of IIEF questions 3 and 4[a] (Studies 148-103 and 148-363).

	N		How often were you able to penetrate your partner?						How often were you able to maintain your erection after penetration?					
	148-103	148-363	148-103			148-363			148-103			148-363		
			Pcbo	Sil	P	Pcbo	Sil	P	Pcbo	Sil	P	Pcbo	Sil	P
Etiology														
Organic	193	91	0.1	1.6	0.0001	0.7	1.5	0.0001	0.2	1.9	0.0001	0.3	2.0	0.0001
Psychogenic	49	100	0.2	2.3	0.0001	0.3	1.5	0.0001	0.3	2.4	0.0001	0.3	1.7	0.0001
Mixed	87	114	0.4	1.9	0.0001	0.7	1.7	0.0001	0.4	2.2	0.0001	0.2	1.8	0.0001
Nocturnal erections														
Yes	202	181	0.2	1.9	0.0001	0.3	1.7	0.0001	0.3	2.2	0.0001	0.3	1.8	0.0001
No	102	112	0.6	2.0	0.0001	0.1	1.7	0.0001	0.4	2.0	0.0001	0.3	1.9	0.0001
Duration														
<3 years	132	134	0.4	1.7	0.0001	0.1	1.9	0.0001	0.3	2.1	0.0001	0.5	1.6	0.0001
>3 years	197	180	0.1	1.9	0.0001	0.3	1.4	0.0001	0.2	2.1	0.0001	0.1	1.9	0.0001
Previous treatment														
Yes	230	255	0.1	1.9	0.0001	0.2	1.7	0.0001	0.2	2.1	0.0001	0.2	1.8	0.0001
No	99	59	0.3	1.5	0.0001	0.3	1.5	0.002	0.3	1.9	0.0001	0.4	1.6	0.02
Diabetes mellitus														
Yes	31	43	0.6	1.6	0.07	0.1	2.1	0.0001	0.3	1.6	0.02	0.0	1.8	0.0001
No	298	269	0.2	1.8	0.0001	0.2	1.6	0.0001	0.3	2.1	0.0001	0.3	1.8	0.0001

a. Reviewers' LOCF analyses; sildenafil-placebo difference in score, after adjustment for baseline and age, classified as <55 or >55.

7.2.3.2.2. Analyses of other IIEF questions

Other aspects of the IIEF were consistent with the effectiveness of sildenafil, as shown in Table 23 below. On all questions except the one pertaining to frequency of desire, the individual studies are consistent and highly statistically significant, so appropriate adjustments for multiple end points are not at issue. with the fixed-dose studies, the sildenafil-placebo difference was much more compelling in the European studies than in the US studies.

Table 23. ITT analyses of supportive IIEF questions at week 12 (titration studies)[a].

Question	Study	Pop'n	Base-line	Placebo		Sildenafil		P[b]
				n	Q	n	Q	
Able to get erection	148-103	Mixed	2.4	138	2.4	138	3.9	<0.0001
	148-363	Mixed	2.2	120	2.4	139	3.8	<0.0001
	148-104	Diabetes	2.0	126	1.8	131	3.1	<0.0001
	148-367	Cord	2.4	156	2.4	153	4.0	<0.0001
Erections hard enough	148-103	Mixed	2.0	138	2.1	138	3.8	<0.0001
	148-363	Mixed	1.9	117	2.1	138	3.6	<0.0001
	148-104	Diabetes	1.6	126	1.8	131	3.1	<0.0001
	148-367	Cord	2.3	155	2.2	154	3.7	<0.0001
Difficulty maintaining erection	148-103	Mixed	1.6	138	1.9	138	3.7	<0.0001
	148-363	Mixed	1.7	113	2.3	134	3.6	<0.0001
	148-104	Diabetes	1.3	127	1.6	131	2.7	<0.0001
	148-367	Cord	1.4	157	1.6	155	3.5	<0.0001
Confidence in erection	148-103	Mixed	1.6	137	1.9	136	3.3	<0.0001
	148-363	Mixed	2.0	120	2.2	137	3.4	<0.0001
	148-104	Diabetes	1.5	127	1.6	131	2.5	<0.0001
	148-367	Cord	1.9	156	1.9	155	3.5	<0.0001
Attempted intercourse	148-103	Mixed	2.2	139	2.9	138	3.5	<0.0001
	148-363	Mixed	2.1	121	2.7	139	2.9	0.4
	148-104	Diabetes	2.0	126	2.7	131	3.4	<0.0001
	148-367	Cord	1.6	158	2.6	155	3.2	<0.0001
Satisfaction of intercourse	148-103	Mixed	1.8	139	2.0	138	3.7	<0.0001
	148-363	Mixed	1.7	121	1.9	136	3.4	<0.0001
	148-104	Diabetes	1.5	127	1.7	131	2.7	<0.0001
	148-367	Cord	1.6	158	1.9	155	3.5	<0.0001
Enjoyment of intercourse	148-103	Mixed	1.9	139	2.2	138	3.6	0.0001
	148-363	Mixed	1.9	121	2.2	138	3.0	<0.0001
	148-104	Diabetes	1.7	126	1.8	131	2.8	<0.0001
	148-367	Cord	1.8	158	2.1	155	3.2	<0.0001
Frequency of ejaculation	148-103	Mixed	2.8	139	2.8	134	3.9	<0.0001
	148-363	Mixed	2.9	120	2.9	138	3.8	<0.0001
	148-104	Diabetes	2.9	127	3.3	131	3.9	0.0006
	148-367	Cord	1.9	155	1.8	152	2.1	0.001
Frequency of orgasm	148-103	Mixed	2.7	139	2.9	138	3.8	<0.0001
	148-363	Mixed	2.6	119	2.7	137	3.7	<0.0001
	148-104	Diabetes	2.9	127	3.3	131	3.7	0.02
	148-367	Cord	1.8	155	1.8	152	2.5	<0.0001

Table 23. ITT analyses of supportive IIEF questions at week 12 (titration studies)[a].*(Continued)*

Question	Study	Pop'n	Base-line	Placebo		Sildenafil		P^b
				n	Q	n	Q	
Frequency of desire	148-103	Mixed	3.6	138	3.5	138	3.5	0.7
	148-363	Mixed	3.2	120	3.4	136	3.6	0.02
	148-104	Diabetes	3.6	127	3.7	131	3.7	0.7
	148-367	Cord	3.7	158	3.3	155	3.7	<0.0001
Rating of desire	148-103	Mixed	3.3	139	3.3	138	2.5	0.006
	148-363	Mixed	3.0	120	3.2	135	3.4	0.08
	148-104	Diabetes	3.3	127	3.4	131	3.5	0.2
	148-367	Cord	3.7	158	3.3	155	3.6	<0.0001
Satisfaction with sex life	148-103	Mixed	1.8	138	2.0	138	3.7	<0.0001
	148-363	Mixed	1.9	120	2.4	138	3.6	<0.0001
	148-104	Diabetes	1.8	127	2.1	131	2.9	<0.0001
	148-367	Cord	2.6	157	2.5	155	3.8	<0.0001
Satisfaction with relationship	148-103	Mixed	2.6	138	2.8	137	4.0	<0.0001
	148-363	Mixed	2.4	117	2.9	137	3.7	<0.0001
	148-104	Diabetes	2.5	127	2.8	130	3.3	0.001
	148-367	Cord	2.9	157	2.9	155	3.9	<0.0001

a. Sponsor's analyses.
b. P-value for non-zero sildenafil-placebo difference.

7.2.3.2.3. Analyses of event logs

The sponsor's analyses of event logs were based upon the proportion of all attempts that were successful. These results are included in some of the study reports.

The reviewers' analyses of event logs, derived from titration studies for which full SAS datasets were available, are summarized in Table 24 below. The results illustrate that subjects in these trials were not profoundly incapacitated. One-third to one-half of subjects had successful intercourse during a treatment-free run-in period. The number of attempts at intercourse was not much affected by the treatment, so the sponsor's analyses of success rates was valid and informative. Whether assessed by the number of successful attempts per subject per week, the proportion of attempts that were successful, or the proportion of subjects who were successful at least once during the study, sildenafil treatment groups had markedly better sexual performance success than did placebo.

Table 24. Successful intercourse by event logs (titration studies).

		Study	Placebo	Sildenafil
Attempts	Total	148-103	5645	5971
		148-363	6984	8978
	Per subject mean	148-103	34	37
		148-363	45	56
	Per subject per week	148-103	2.8	3.1
		148-363	1.7	2.2

Table 24. Successful intercourse by event logs (titration studies).*(Continued)*

		Study	Placebo	Sildenafil
Successes	Total	148-103	732	2792
		148-363	1780	5284
	Per subject mean	148-103	4.4	17
		148-363	11	33
	Per subject per week	148-103	0.4	1.4
		148-363	0.4	1.3
Success by attempts	(%)	148-103	13	47
		148-363	25	59
Success by subjects (%)	During run-in	148-103	37	32
		148-363	33	38
	Double-blind period	148-103	55	87
		148-363	63	89

7.3. Summary of key effectiveness findings

7.3.1. Mechanism of action

In the absence of (intentional) excitatory sensory stimulation, penile erections were only infrequently reported in association with sildenafil. Studies of erectile function by penile plethysmography showed that sildenafil administration, accompanied by visual sexual stimulation or mechanical stimulation, was associated with more frequent and longer duration erections than was placebo. These studies do not address the molecular or receptor-mediated mechanisms of sildenafil, but they provide a plausible basis for findings in studies of effectiveness with respect to sexual intercourse.

7.3.2. Dose-dependent effects

Multiple-single-dose crossover studies of erectile function by penile plethysmography showed that doses of 25 to 100 mg were more effective in producing erections than was placebo. The data suggest that 25 mg is not the smallest dose with a detectable effect in a small study, and that 100 mg is not associated with the largest attainable effect.

Parallel, placebo-controlled studies of sexual function leave no doubt that 25 to 100 mg are effective doses, as assessed by a validated sexual function questionnaire. Further, these studies strongly support a monotonic relationship to dose: placebo < 25 mg < 50 mg < 100 mg. One study is consistent with 200 mg being not differentiable from 100 mg. The 25-mg-placebo difference is more than half of the 100-mg-placebo difference; this suggests that the 25-mg dose is already fairly high on the dose-response curve.

Event log data, analyzed by various means, and IIEF questions relating to erectile function and (male) sexual satisfaction are highly internally consistent with findings pertaining to sexual performance. Quality-of-life questions afield of sexual performance tended to show no effect.

In titration studies, subjects generally took the first opportunity to migrate from a starting dose of 25 or 50 mg to a higher dose. Few subjects discontinued use of sildenafil for lack of effectiveness. The proportion of subjects remaining on various available dose levels varied for study to study, quite likely dependent upon the etiology of the erectile dysfunction.

7.3.3. Time course of effects

7.3.3.1. Time course after a dose

This was not well studied. In principle, it should have been possible to estimate the success rate as a function of time after dosing in titration studies (148-103 and 148-363). However, the case report forms captured neither the time of dosing nor the time of sexual activity.

7.3.3.2. Time course with repeated dosing

Studies 148-102 and 148-363 had evaluations of IIEF questions at 3 and 6 months. The sponsor's LOCF analyses (although not optimal for this assessment) do not suggest a waning of effectiveness over this interval.

The long-term open-label experience demonstrates a low rate of withdrawal for any reason.

7.3.4. Effectiveness in sub-groups

7.3.4.1. Non-specific organic etiology

In general, this category included vascular and neurological etiology, including diabetes, but not spinal cord injury or anatomical defects. The reviewers carried out analyses of the primary effectiveness questions in the subset of subjects with 'organic' erectile dysfunction in 4 studies, as shown in Table 25 below. Although the 'organic' category is not well characterized, the effectiveness of sildenafil is not in doubt.

Table 25. Effectiveness in organic erectile dysfunction.

	Fixed-dose studies				Titration studies					
	148-102 N=411		148-364 N=165		148-103 N=193			148-363 N=91		
	Slope	*P*	Slope	*P*	Pcbo	Sil	*P*	Pcbo	Sil	*P*
How often were you able to penetrate your partner?	16±2	0.0001	13±3	0.0001	0.1	1.6	0.0001	0.7	1.5	0.0001
How often were you able to maintain your erection after penetration?	15±2	0.0001	15±3	0.0001	0.2	1.9	0.0001	0.3	2.0	0.0001

7.3.4.2. Psychogenic etiology

Study 148-355[12] was a randomized, double-blind, 4-week, 2-period, placebo-controlled, flexible-titration, crossover study in 44 subjects with erectile dysfunction of no established organic cause. The primary end points included the *fraction* of erections adequate for intercourse. The *number* of such erections, analyzed by the sponsor, was highly statistically significantly greater on sildenafil.

The reviewers carried out analyses of the primary effectiveness questions in the subset of subjects with psychogenic erectile dysfunction in 4 studies, as shown in Table 26 below. There can be little doubt that sildenafil is effective in treating erectile dysfunction of psychogenic etiology.

Table 26. Effectiveness in psychogenic erectile dysfunction.

	Fixed-dose studies				Titration studies					
	148-102 N=50		148-364 N=129		148-103 N=49			148-363 N=100		
	Slope	*P*	Slope	*P*	Pcbo	Sil	*P*	Pcbo	Sil	*P*
How often were you able to penetrate your partner?	23±5	0.0001	15±3	0.0001	0.2	2.3	0.0001	0.3	1.5	0.0001
How often were you able to maintain your erection after penetration?	28±5	0.0001	15±3	0.0001	0.3	2.4	0.0001	0.3	1.7	0.0001

12. *Study 148-355: A double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of sildenafil (UK-92,480) (taken when required over a 28 day period) in patients with erectile dysfunction with no established organic cause.* on page 191.

7.3.4.3. Diabetes

Study 148-104[13] was a randomized, double-blind, parallel, placebo-controlled, flexible-titration study in 268 subjects with well-controlled type I or type II diabetes and erectile dysfunction. The primary end points were the 2 IIEF questions pertaining to sexual performance. Subjects began on sildenafil 50 mg and at the first opportunity, mre than 75% migrated to the 100-mg dose. The results of the primary effectiveness analyses are reproduced in Table 27 below[14].

Table 27. ITT analyses of IIEF questions 3 and 4 (Study 148-104).

		Placebo N=132		Sildenafil N=136		*P*
		n	Q	n	Q	
How often were you able to penetrate your partner?	Baseline	—	1.7[a]	—	—	
	Week 12	126	2.0	131	3.2	<0.0001
How often were you able to maintain your erection after penetration?	Baseline	—	1.4	—	—	
	Week 12	125	1.6	131	2.9	<0.0001

a. Pooled baseline value for all subjects.

The reviewers carried out analyses of the primary effectiveness questions in the subset of subjects with erectile dysfunction and diabetes in 4 studies, as shown in Table 28 below. There were fewer such subjects than subjects with psychogenic dysfunction, but not many fewer. Both of the questions for all 4 studies (8 comparisons) lean in the direction of showing a benefit to sildenafil, but the magnitude of the effect is clearly not very large[15].

Table 28. Effectiveness in diabetics with erectile dysfunction.

	Fixed-dose studies				Titration studies					
	148-102 N=72		148-364 N=44		148-103 N=31			148-363 N=43		
	Slope	*P*	Slope	*P*	Pcbo	Sil	*P*	Pcbo	Sil	*P*
How often were you able to penetrate your partner?	5±5	0.29	2±5	0.72	0.6	1.6	0.07	0.1	2.1	0.0001
How often were you able to maintain your erection after penetration?	8±5	0.11	5±4	0.26	0.3	1.6	0.02	0.0	1.8	0.0001

7.3.4.4. Spinal cord trauma

Study 148-358[16] was 2 studies conducted in the same population of 27 subjects with a history of spinal cord trauma preserving an erectile response to a vibrator. The first phase was a randomized, double-blind, 2-period (placebo and sildenafil 50 mg), single-dose crossover study in which subjects underwent penile plethysmography in the clinic. The proportion of subjects attaining an erection with >60% rigidity was 4% on placebo and 46% on sildenafil. The second phase was a randomized, double-blind, parallel, placebo-controlled study over 4 weeks of use at home, with interest in continued use of the drug being the primary end point. The proportion of successful intercourse attempts, as assessed by the sponsor, was 38% on placebo vs. 67% on sildenafil.

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13. *Study 148-104: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male diabetic patients with erectile dysfunction.* on page 118
14. Same as Table 92 on page 121.
15. 'Large' being difficult to interpret where numerical values have been assigned to categorical responses.
16. *Study 148-358: A two stage, double blind, placebo-controlled study to assess the efficacy and safety of oral doses of sildenafil (UK-92,480) in spinal cord injury patients with erectile dysfunction.* on page 197.

Study 148-367[17] was a randomized, double-blind, 2-period (placebo and sildenafil 50-100 mg), 6-week, crossover study in 89 subjects with traumatic spinal cord injury. The primary end point was election of the preferred treatment, but subjects also filled out the IIEF. For both IIEF questions pertaining to sexual performance, highly statistically significant improvements were observed on sildenafil, and all other IIEF supporting questions showed similar, highly internally consistent effects.

Spinal cord injury was a specific exclusion from other studies of effectiveness.

7.3.4.5. Blacks

The sponsor performed analyses of IIEF sexual performance questions by race and found a significant interaction (p=0.005 and p=0.02[18]) in flexible-dose studies (148-103 and 148-363), in which about 6% of subjects were non-Caucasian. Similar analyses in fixed-dose studies (148-102 and 148-364) showed no statistically significant effect (p=0.18[19]). The sponsor's larger meta-analyses of 8 studies[20], reviewed in no detail, also showed no significant effect of race (p=0.87 and p=0.92).

The reviewers performed no analyses of effectiveness by race.

The sponsor's meta-analyses of 8 studies[21], reviewed in no detail, showed no significant effect of race (p=0.31 and p=0.91).

7.3.4.6. Elderly

The reviewers' sub-group analyses of IIEF sexual performance questions in studies 148-102, 148-103, 148-363, and 148-364 showed nominally statistically significant interactions with age in about half of the comparisons.

The reviewers conclude that if there is an effect of age, it is not of clinically significant magnitude.

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17. *Study 148-367: A double-blind, randomised, placebo-controlled, two way cross-over, flexible dose study to assess the efficacy and safety of oral doses of sildenafil in patients with erectile dysfunction caused by traumatic injuries to the spinal cord.* on page 218.
18. These are the p-values for the IIEF questions. The sponsor's presentation does not indicate in which treatment group sildenafil appears to be more effective.
19. Applies to 'frequency of penetration' question only.
20. Studies 148-101/101B, 148-102, 148-103, 148-104, 148-106, 148-359, 148-363, and 148-364.
21. Studies 148-101/101B, 148-102, 148-103, 148-104, 148-106, 148-359, 148-363, and 148-364.